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RESEARCH ARTICLE

COLLAGEN.

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Abstract

A paper explores properties, structure and characteristics of collagen. The molecule of this protein is an important part of connective tissues, bones, skin and the walls of blood vessel. The types of collagen and their structure are also discussed. Diseases and genetic defects that are connected with the problems of collagen synthesis in the human body are examined. Special attention is paid to the Marfan's syndrome as one of the most common diseases connected with collagen synthesis.

Introduction:-

Collagen is the fibrillar protein that is the main component of the connective tissue. It provides the strength and elasticity of the tissue. Collagen is the main protein that many-celled animals have in their bodies. The body of mammals, for instance, contains 25-35 % of collagen. Human body contains 21 collagen types (Harvey 2011: 87).

All types of collagen play structural and functional role in the extracellular matrix of the connective tissue. The extracellular matrix supports tissues from the outside and provides it with the specific mechanic and physicochemical properties (Nicotra 2008: 250). The structure created by collagen interacts with different types of molecules and receptors (Swamy et al. 2011: 399). It creates a structure to which other proteins and minerals can connect or "stick". It explains the origin of the term "collagen" that may be translated from Greek as "producing glue".

Collagen has triple-helical structure that consists of three coiled peptide chains (Fig. 1). The peptide chain contains the certain sequence of the amino-acids. The main component in the chain is glycine, which is almost every third amino-acid in the chain. The helical structures form microfibers that further create macrofibes. Created structures depend on collagen type (Shoulders and Raines 2009: 935).

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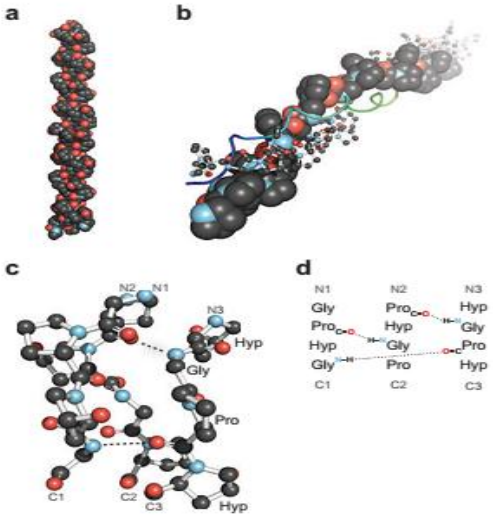
Figure 1:- Triple-helical structure of collagen.



Source: Shoulders

Collagen is used in many spheres: from the food industry to medicine. The first known product obtained from collagen is gelatine. It is used to produce different food, as well as in pharmaceutics, cosmetics, and photography (Shoulders and Raines 2009: 945).

The first glue that was used in the industry was animal glue containing collagen. Such a glues may soften after reheating. It is a reason for their use in production of musical instruments that can be reopened for repairmen. Collagen is also used for the production of musical strings (Nicotra 2008: 255).

The sphere where collagen is widely used is medicine. Collagen is used in cosmetic medicine, surgery, wound and burn care. This protein is used as a dermal filler or the component for the prevention of skin aging (Shoulders and Raines 2009: 946).

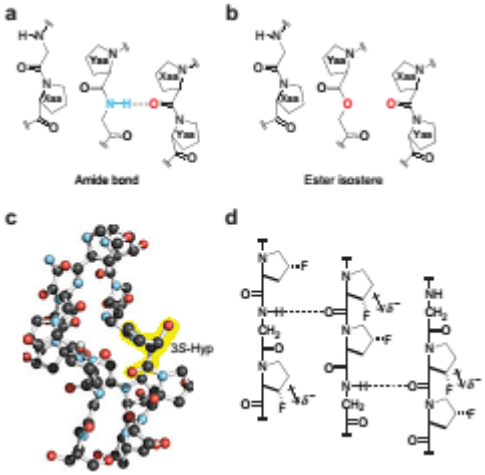
It is important to understand the process of collagen synthesis. Collagen synthesised in the human body creates a structure of bones, vessels, and skin. Problems during the synthesis of collagen types lead to the serious diseases (Ehler-Danlos syndrome, Marfan's syndrome, osteogenesis imperfecta) (Yalovac and Ulusu 2007: 140). On the other hand, biochemistry helps to synthesise materials with the structure similar to collagen for medical applications (Shoulders and Raines 2009: 946). The understanding of collagen synthesis mechanisms gives the possibility to use a proper therapy for every disease, as well as to use these mechanisms in new technologies.

The chemistry of the Molecule:-

Collagen triple helix consists of two similar polypeptide chains (α1 chains) and one slightly different chain (α2 chain). Every chain contains the sequence of amino acids where every third component is glycine. The second amino acid is proline. Two abovementioned components are important for the creation of the helical conformation. Other acids (alanine, lysine, alanine, etc.) are met rarely depending on the structure (Van der Rest and Garrone 1991: 2816).

Apart from fibre structure, one of the collagen features is hydroxylation of proline and lysine. This process takes place after the incorporation of these amino acids into the polypeptide chain. Hydroxyproline and hydroxylysine play the important role in the stability of the triple helix (Fig. 2). The stability of helical structure is connected with the hydrogen bonds that are created between the hydroxyl group of one chain and the hydrogen atom of another chain (Talwar and Srivastava 2006: 87).

Figure 2:- Hydrogen bonds in the collagen molecule.



Source: Shoulders

Hydroxyl group of hydroxylysine can be glycosylated due to the enzymes action. Typically disaccharides glucose or galactose are attached to the polypeptide chain. This process takes place before the formation of the triple helix structure (Shoulders and Raines 2009: 935).

Typical sequence of amino acid residues in the polypeptide chain is –Gly-X-Y- (or –Gly-Pro-Y- and –Gly-X-Hyp-) where Gly stands for glycine, Pro stands for proline, and Hyp stand for hydroxyproline. Other amino acid residues are rare. Therefore, the most of the α-chain can be represented by the formula $(–Gly-Pro-Hyp-)_{333}$ (Talwar and Srivastava 2006: 87). There are peptide bonds within the chain and hydrogen bonds between chains. The presence of hydroxyl groups makes possible the creation of the hydrogen bonds between separate triple helixes, thus, forming bigger fibres (Van der Rest and Garrone 1991: 2820).

Table 1:- Amino Acid Compositions for Various Collagen Chains

	α1(I)	**α2(I)**	**α1(II)**	**α1(III)**	**α1(IV)**	**α1(VI)**	**α1(VII)**	**α1(X)**
Hyp	117	113	93	144	219	34	159	74
Asp	34	33	26	28	58	71	145	12
Asn	11	12	25	24	16	28	27	13
Thr	17	22	20	15	43	39	131	24
Ser	39	30	32	45	70	52	166	26
Glu	49	55	45	48	68	68	187	22
Gln	30	42	22	26	73	40	105	22
Gly	347	351	352	367	477	156	626	174
Ala	122	106	106	94	53	72	189	36
Pro	123	115	109	96	104	56	267	69
Cys	0	0	0	2	20	19	16	1
Val	20	19	40	15	50	65	200	24
Met	7	11	5	9	30	10	17	10
Ile	7	12	17	15	58	42	55	26
Leu	21	28	33	22	84	66	207	29
Phe	15	14	13	8	46	33	39	14
Tyr	4	2	5	5	18	28	36	21
His	3	2	13	7	14	14	28	9
Lys	38	39	31	39	93	54	93	35
Arg	53	54	55	48	43	59	216	19
Trp	0	0	0	0	5	3	19	2
Residues (total)	1057	1060	1042	1057	1642	1009	2928	662
Residues (triple helix)	1014	1014	1014	1029	1268	336	1531	463

Source: Talwar and Srivastava

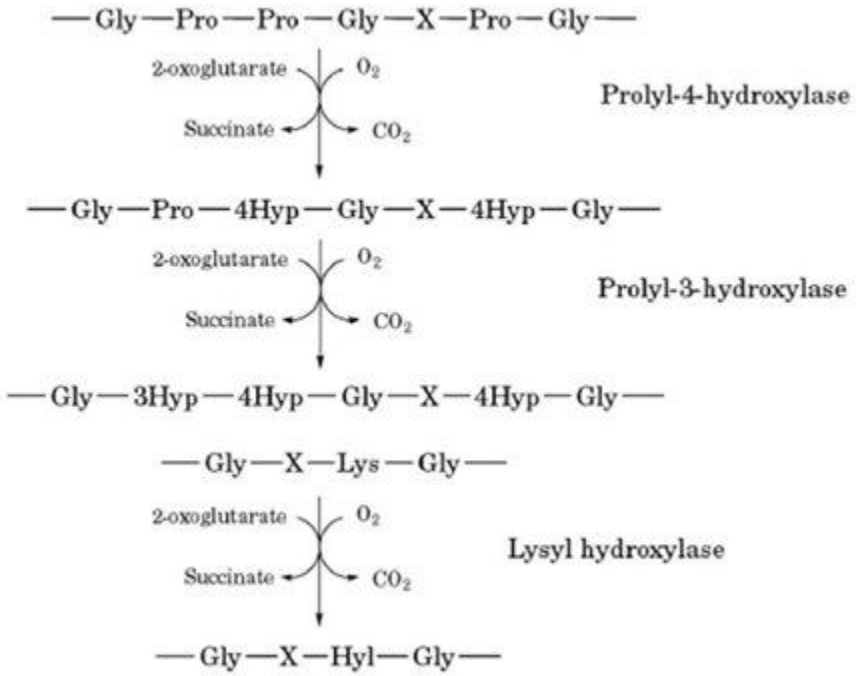
The synthesis of the Molecule:-
The synthesis of collagen is a complex biochemical process. It includes intracellular and extracellular stages. The formation of the peptide chains, hydroxylation and glycosylation are performed within the cells. The formation of collagen fibrils and cross-linked structures is performed outside the cells (Shu-Tung Li. 2000: 320).

Intracellular Stage :-
There are different 40 genes that code different collagen chains. The genes are located on 15 different chromosomes. Each gene codes specific mRNA section. The synthesis is started with turning on genes associated with the formation of the specific peptide chain (Talwar and Srivastava 2006: 95).

The mRNA exits the nucleus into the cytoplasm. The translation products are directed into the endoplasmic reticulum (ER). ER is directed by a hydrophobic N-terminal signal sequence. This signal interacts with a signal recognition particle that binds to an ER-docking protein. After the release of the particle further translation is performed. Membrane peptidase splits signal peptide. The product of the cleavage is a pre-pro-collagen chain that includes pro-domains and the helical domain (Van der Rest and Garrone 1991: 2822).

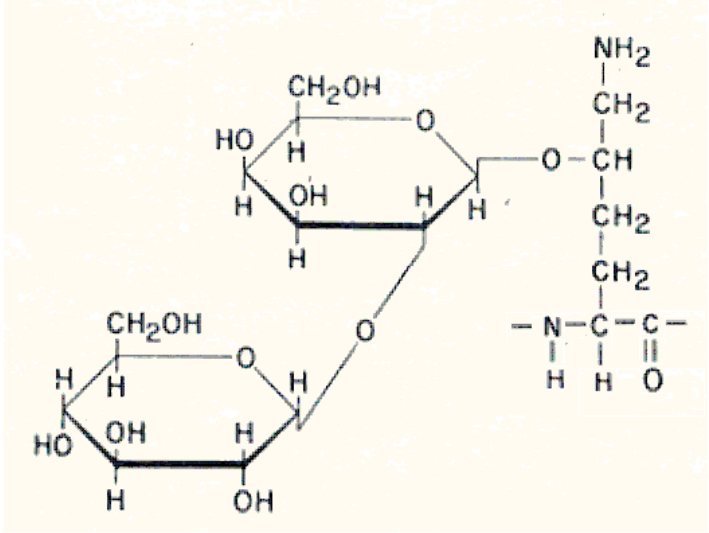
Several important intracellular modifications are performed within the ER. One of the main processes is the specific hydroxylation of Pro and Lys residues. Lysylhydroxylase, prolyl-4-hydroxylase, and prolyl-3-hydroxylase are the necessary enzymes of this process. Lysylhydroxylase and prolyl-4-hydroxylase interact with X-Lys-Gly and X-Pro-Gly sequences, and prolyl-3-hydroxylase interacts with Pro-4-Hyp-Gly sequences (Fig. 3). This process also needs vitamin C. The presence of 4-Hyp plays key role in the stability of the obtained collagen (Penkova et al. 1999: 398). The other process is glycosylation of the certain hydroxylysine residues in the helical structure. Two specific glycosidases are required for the process. The first enzyme ads galactose to certain hydroxylysine residues, the second adds glucose to galactosyl-hydroxylysine (Fig. 4). All these enzyme processes take place only before the coiling of individual chains into a triple helix. This structure is known as pro-collagen (Camp et al. 2011: 4374).

Figure 3:- Obtaining of hydroxyproline and hydroxylysine by the action of the prolyl and lysyl hydroxylases that require molecular oxygen, ascorbic acid (vitamin C) and α-keto (oxo) glutarate for their action.



Source: http://www.namrata.co/collagen-synthesistypes-and-composition-part-2/

Figure 4:- The galactose and glucose residues added sequentially by galactosyl and glucosyl transferases.



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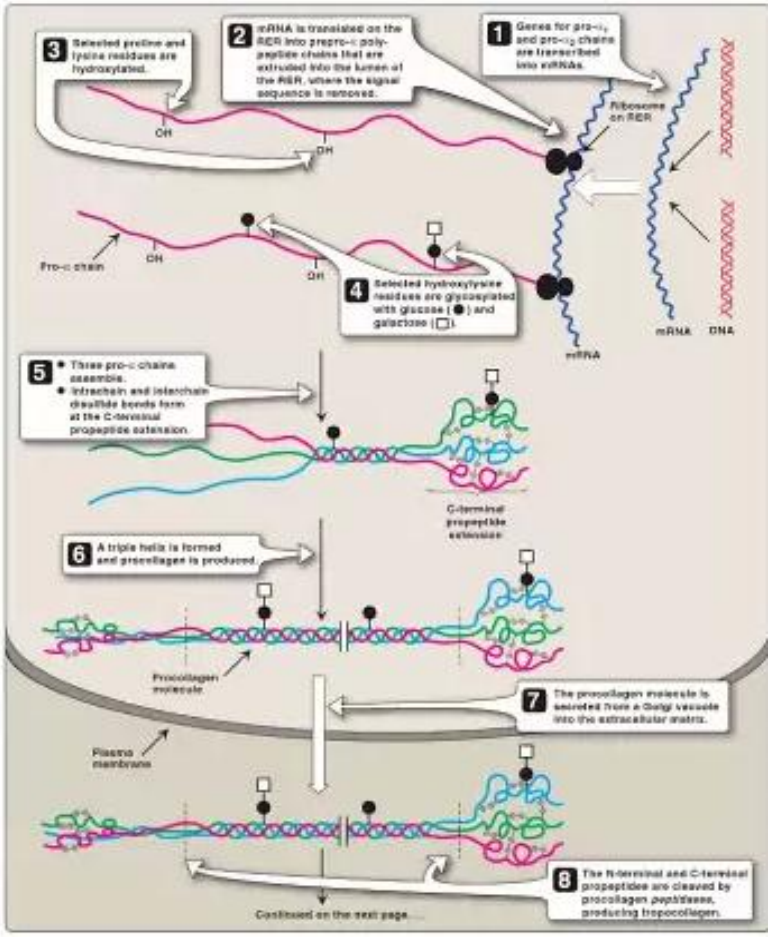
The pro-collagen is packed into a transfer vesicle and transferred to the Golgi apparatus. In the Golgi apparatus, oligosaccharides are added to the pro-collagen during the last post-translational modification. After adding of oligosaccharides, the pro-collagen is packaged into a secretory vesicle and destined for the extracellular space (Moody et al. 2003: 998).

Some cells may produce more than one collagen type. For such cells, appropriate chain recognition and assembly play the main role in the formation of correct functional collagens. The other processes, like recognition at the C-terminal domains, take place. During synthesis of almost all collagens, the initial interaction between C-pro-peptide domains occurs before the triple helix formation. Before the formation of trimeric structure the pro-peptide domains are stabilized by intrachain disulphide bonds. The process is catalysed by protein disulphide isomerase. After the formation of the interchain disulphide bonds the folding of the helical domain takes place. The effectiveness and stability of this process requires formation of hydroxyproline before the nucleation. Efficient triple helix formation then needs acceleration of the rate-limiting isomerization of Pro residues by the enzyme prolyl isomerase (Shoulders and Raines 2009: 936).

Extracellular Stage:-

Folded molecules of the pro-collagen are transported from the ER through the Golgi complex (Fig. 5). Afterward, the molecules are packaged into secretory vacuoles, which release collagen from the cell surface by the process called endocytosis. On this stage, the pro-peptide domains are removed from the interstitial pro-collagens by specific N- and C-pro-collagen proteases. For other collagens, for example for the type V collagen, pro-domains are generally reserved. For the most collagens the C-pro-peptide is almost always removed, but the N-pro-peptide may stay. Possibly it is connected with the control of fibril growth. The obtained substance is called tropocollagen (Harvey 2011: 90).

Figure 5:- The steps of collagen synthesis and formation of mature collagen



Source : Harvey

Then the process of formation of functional fibrils is performed. The processes is not well understood. Different studied of fibril formation based on the analyses of pepsin- or acid soluble collagen permitted to identify different phases in fibril growth. This process includes nucleation during a lag phase that is followed by a growth phase. The experimental results also permitted to conclude that the telopeptides are important components of fibrillogenesis (Fratzl 2008: 122). Possibly the C-telopeptide is connected with the specific region of a collagen fibril when new collagen molecules is added (Fratzl 2008: 124).

The next step of collagen synthesis is the cross-linking. Functional tissues are formed during this process. The process also provides the strength to tissues. Small amounts of soluble collagen are extracted from tissues. The cross-linking process is performed very fast. The extensive network between all collagen molecules is create due to this process (Shoulders and Raines 2009: 931).

The cross-linking process starts from the formation of allysine and/or hydroxyallysine from specific Lys residues in the telopeptides of the interstitial collagens. The specific enzyme, called lysyl oxidase, is necessary for the process. These substances form initial functional cross-links. The products can be both the results of aldol condensation or aldimine (ketoamine) links. The aldimine (ketoamine) involves specific lysine or hydroxylysine residues from the telopeptides or from the helical domain of the collagen (Shoulders and Raines 2009: 932).

The formation of the specific collagen type, as well as its structure, requires the certain temporal, spatial, and quantitative regulation of collagen biosynthesis. The process and degree of collagen production is sensitive to the effect of the various units, like growth factors and cytokines. For example gene transcription process depends on the presence of different cis-acting promoters, enhancers, and silencers. According to the research results, pro-peptide

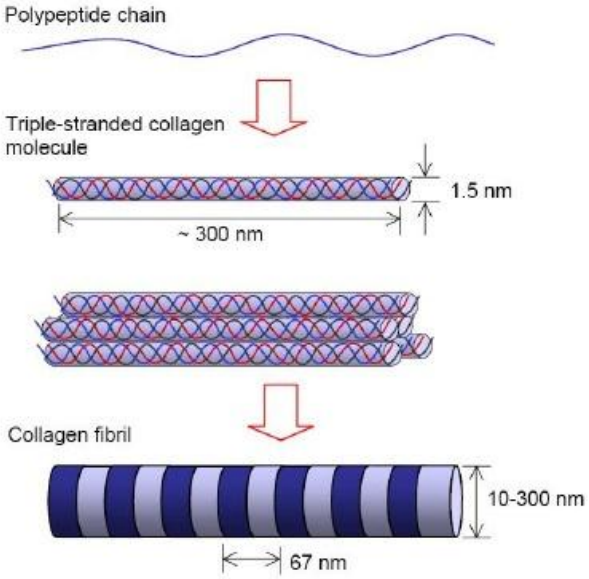
parts that are released during secretion and fibril formation may play a role in the control of collagen production, possibly through the translational control (Swamy et al. 2011: 405).

Molecular structure of Collagen:-

As it was mentioned above, collagen consists of three polypeptides (α-chains). Each chain has a general amino acid sequence of (-Gly-X-Y-). In most cases, X is proline and Y is hydroxyproline. The research results permitted to create the initial triple-helical model. Afterward the model of modified triple helix of the collagen molecule was proposed. The scientists came to the conclusion that collagen is a protein which has a typical triple helix structure that extends over the main part of the molecule. The triple helix contains glycine in every third place. Glycine in the polypeptide chains is always situated inside the helix. Proline (hydroxyproline) and lysine (hydroxylysine) residues are situated at the surface of the helix. Proline and hydroxyproline are the necessary elements that permit to form the structure and to stabilize the triple helix. At present time, 19 proteins are known as collagen. Type I collagen is the most abundant. It is the main component of bones, skin, ligament, and tendon (Shu-Tung Li. 2000: 325).

A collagen molecule (also known as tropocollagen) has a molecular weight of about 283,000 daltons. For the type I collagen, the molecule has a length of about 280 nm and a diameter of about 1.5 nm. The conformation is similar to a rigid rod. Its three left-handed helical polypeptide chains form are intertwined and form a right-handed helix around a central molecular axis. Two of the polypeptide chains are equal (α1) and have 1056 amino acid residues. The third polypeptide chain (α2) has 1029 amino acid residues. A rise per residue within the triple-helical structure is 0.286 nm approximately. The unit twist is 108°. It has 10 residues in three turns and a helical slope (repeating distance within a single chain) that comprises 30 residues of 8.68 nm length (Fig. 6). The main part of the amino acids have the sequence of Gly-X-Y. The rest of the molecule does not have the sequence of Gly-X-Y. These parts are nonhelical, and its content varies for the different collagen types. The nonhelical parts of the molecule are located at the N- and C-terminal ends (Shu-Tung Li. 2000: 328).

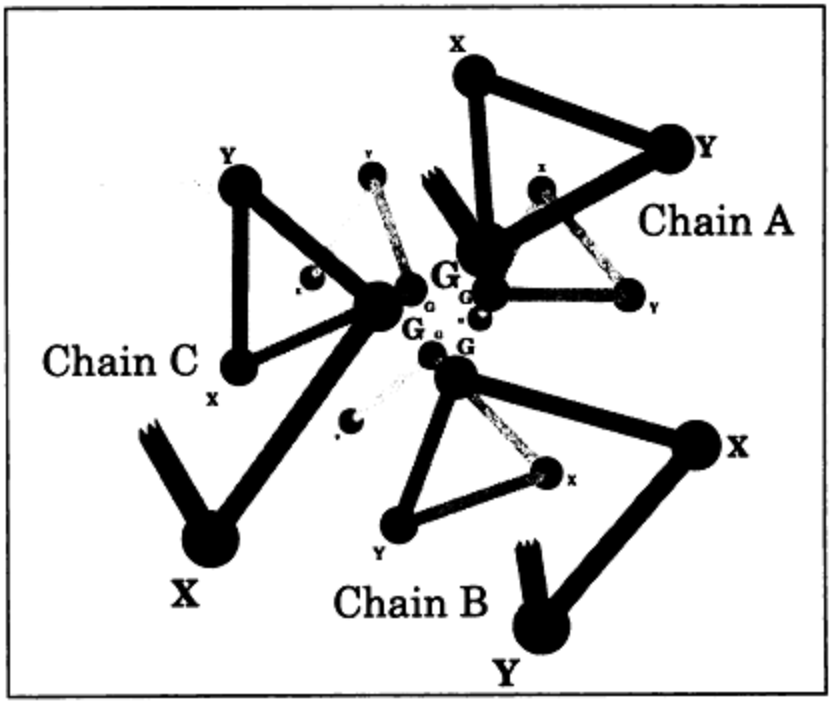
Figure 6 :- Collagen structure



Source : http://www.namrata.co/collagen-synthesistypes-and-composition-part-2/

The stability of the triple-helical structure of a collagen molecule can be explained by the following factors: (1) a tight fit of the amino acids within the triple-helix (Fig.7); (2) the formation of the interchain hydrogen bond between the backbone carbonyl and the interactions of amino hydrogen; and (3) the contribution of water molecules to the interchain hydrogen bond formation ((Shu-Tung Li. 2000: 328).

Figure 7 Cross-section of the triple helix



Source: Van der Rest & Garrone

Intermolecular crosslinks are formed in the telopeptide parts of the molecule. As a rule, common crosslinks between molecules are formed between an allysine of one telopeptide of one molecule, which the ε-amino group of lysine or hydroxy-lysine converted to an aldehyde, and an ε-amino group of a lysine or hydroxylysine in the triple helix or a second molecule.

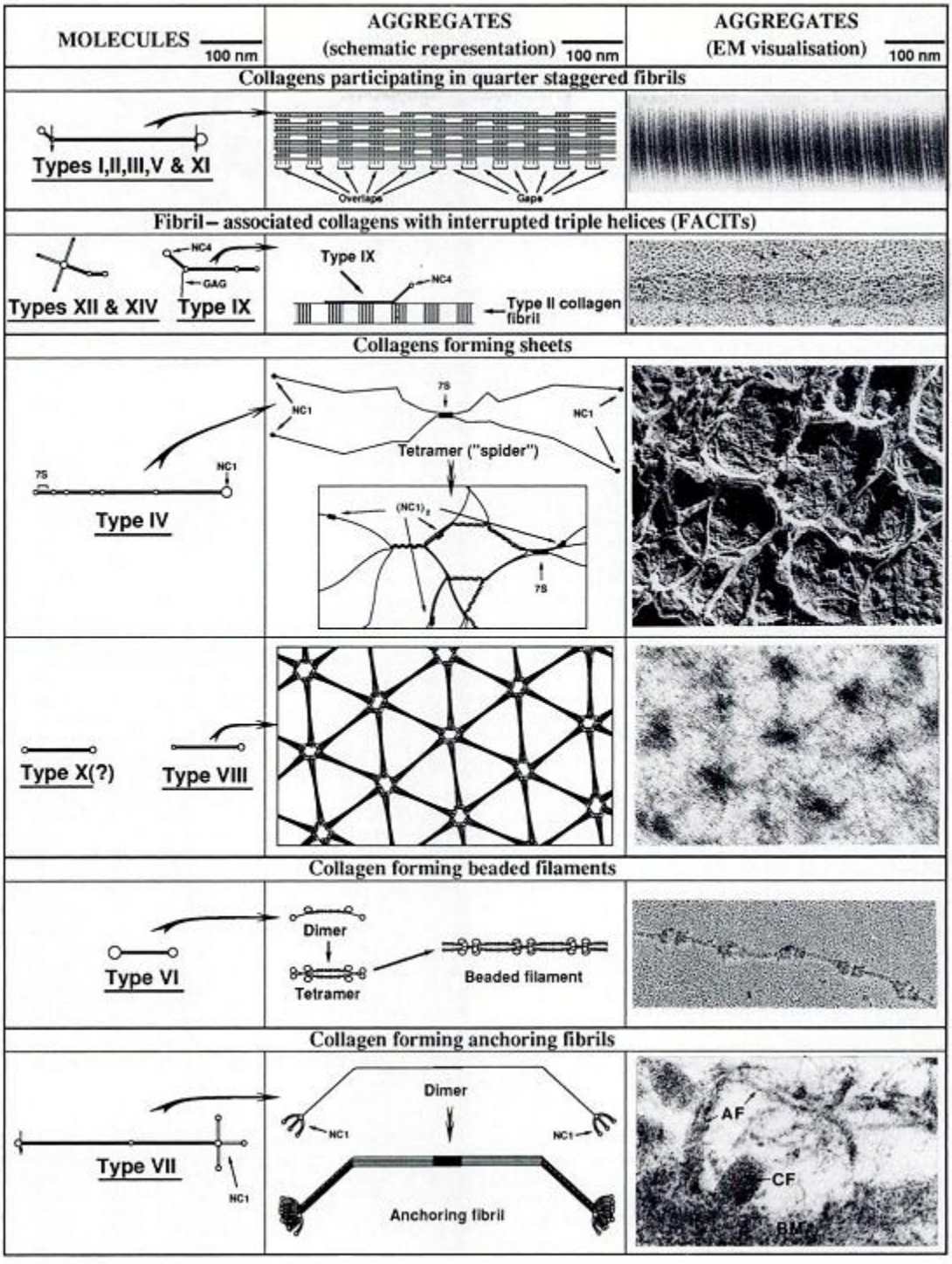
Collagen tends to the creation of the aggregates. The size of these aggregates depends on the tissue and age. It is about 50-300 nm in diameter. The fibrils form larger fibre structures. Collagen molecules are organized in specific orders both longitudinally and in cross-section, and this order of collagen molecules in a fibril depends on the tissue (Shu-Tung Li. 2000: 329).

Approximately equal number of acidic (aspartic and glutamic acids) and basic (lysine and arginine) side groups in the molecule is the important structural aspect of collagen. These groups are charged under physiological conditions, and the collagen is electrically neutral. However, the different parts of the collagen molecules contain the charged groups. The presence of these groups leads to the formation of intra and intermolecular hydrogen-bonded salt-linkages (Pr-COO–+H3N-Pr). Furthermore, these groups of amino acids are nonpolar (for example, alanine (Ala), valine (Val), leucine (Leu), isoleucine (Ile), proline (Pro), and phenolalanine (Phe)) and hydrophobic. The chains with the abovementioned amino acids do not contact with water molecules and interact with the nonpolar chains of amino acids. It leads to the creation of the hydrophobic parts within collagen fibrils. This process in various tissues includes intermolecular interactions, both the electrostatic and hydrophobic (Krahn et al. 2006: 182).

Apart from the collagens with the fibrillar structure there are another collagen structures. For example, some collagen types have fibril-associated structure with interrupted triple helices (FACIT). There are three main parts within the molecule of such a collagen. The first part contains one or two helical regions that serve for the adhesion of the molecule to the fibrils. The second part contains another helical region that protects out of the third part. The third part does not contain helical structures and serves for the interactions with the other elements. Triple helical parts are interrupted with the non-helical parts (Shu-Tung Li. 2000: 331).

Scientists also discovered several nonfibrillar structures (Fig. 8). For example, some collagen types can form a sheet or membrane. The structure may look like a network of cords that are connected together and can entrap large complexes. These sheets may also form the protective or adhesive layers (Van der Rest and Garrone1991: 2816).

Figure 8:- Types of Collagen structure.



Source: Van der Rest & Garrone

The other structure is beaded filaments. In this case, the protein contains very short triple helical parts. A single cysteine or cysteine chain is situated within this part. The clusters of cysteine form intramolecular bonds at the ends of the helix. The presence of two imperfections within the triple helix is typical for this structure (Van der Rest and Garrone1991: 2817).

One more structure is collagen forming anchoring fibrils. This structure contains significantly long (about 420 nm) triple helical part. The end of this part contains NH_2-terminal fragments and the COOH-terminal P2 fragment. A very large nontriple helical NC1 domain is situated at the COOH-terminal end of the molecule. This domain contains three -50 nm arms terminated by small globules. A smaller globular NC2 domain is situated at the amino end (Van der Rest and Garrone1991: 2818).

Types of Collagen:-

There are 28 collagen types known by the scientists. 21 types of collagen are present within the human body. Every collagen type is encoded for by a specific gene. The various types of collagens have almost the same sequence of amino acids (-Gly-X-Y-). However, the content of different amino acids within the structures varies depending on the collagen type. Different collagen types are also situated in different parts of the human body. Collagen types may be divided in two groups: fibrillar and nonfibrillar (Van der Rest and Garrone1991: 2815). The table 2 shows the places where certain collagen types are located within the human body.

Table 3:- Collagen types and their presence in the human body

Type	Representative tissues
Fibrillar collagens	
I	Skin, bone, tendon, dentin
II	Hyaline cartilage, vitreous body
III	Skin, vessels
V	Hamster lung cell cultures, fetal membranes, skin, bone, placenta, synovial membranes
XI	Hyaline cartilage
Nonfibrillar collagens	
IV	Basement membranes, glomerular basement membrane
VI	Vessels, skin, intervertebral disc
VII	Dermoepidermal junction
VIII	Descemet's membrane, endothelial cells
IX	Hyaline cartilage, vitreous humour
IX	Hyaline cartilage, vitreous humour
X	Growth plate
XII	Embryonic tendon and skin, periodontal ligament
XIII	Endothelial cells
XIV	Fetal skin and tendon

Source: Van der Rest & Garrone

The most common collagen types are the following: (1) type I, which is found in all tissues and organs; (2) type II, which is the component of cartilage (3) type III, which is present in skin, blood vessels, and organs tissues. The high content of this collagen has the body of young persons; (4) type IV, which is the main nonfibrillar collagen; (5) type V, which is fibrillar collagen present in all tissues as a component of cytoskeleton (Nicotra 2008: 262).

Type I collagen is the main collagen in the human body. Almost 90 % of all collagen is type I. Tendon and bones, as well as skin, lung, fascia, heart valves, scar tissue, cornea, and liver contain collagen I. It is a component that determines the tensile strength of bones. Bone density, its size and shape depend on the content and distribution of the collagen I fibres (Talwar and Srivastava 2006: 95).

Type II collagen is the protein present in the cartilaginous tissues. Compared with type I collagen, type II collagen has the higher O-glycosylation of hydroxylysyl residues (Talwar and Srivastava 2006: 97).

Type III collagen is a component of skin, blood vessels and viscera. The body of adult person (particularly the skin) contains about 80 % of type I and 20 % of type III collagen. The body of newborns contains more type III collagen. Possibly, the soft and elastic skin of the newborn, the flexibility of the blood vessels can be partially explained by the presence of type III collagen (Talwar and Srivastava 2006: 98).

Type IV collagen is a component of the basement membranes and basal lamina structures. The network structure of collagen IV permits to form the filtration system. Such a system in the lens capsule of the eye helps to perform the

light filtration. The glomerular basement membrane of the kidney is responsible for the blood filtration and for the removal of waste products. The basement membrane of the capillaries controls the association of oxygen and nutrients into the tissues (Talwar and Srivastava 2006: 98).

Type V collagen is present in almost all tissues. It is associated with collagens I and III. It functions as a cytoskeleton because collagen V is a component of intercellular space. Compared to other tissues, the most of collagen V is in the intestine (Talwar and Srivastava 2006: 98).

The other types of collagen are met less often in the human body. Their structures are similar to the structures of collagens I-V. These collagens may have fibrillar, sheet, sponge, FACIT structures or structures with anchoring fibrils.

Diseases and genetic Defects:-

The disruption of the collagen synthesis may lead to the various diseases. The most of diseases is caused by the mutations on the genes coding the biosynthesis process. Osteogenesis imperfecta, chondroplasias, Ehlers-Danlos syndrome, Alport syndrome, Bethlem myopathy, epidermolysis bullosa, Knobloch syndrome, osteoporosis, arterial aneurysms, osteoarthritis, and intervertebral disc diseases are the typical examples (Yalovac and Ulusu 2007: 139). Table 3 presents the main diseases caused by different mutations. However, aging and vitamin deficiency (especially vitamin C) can also disrupt the collagen synthesis and lead to the diseases development (Myllyharju and Kivirikko 2001: 8). The main health problems connected with the collagen synthesis are discussed below.

Table 3:- The Involvement of Different Collagen Chains in Genetic Diseases

Collagen type	Chain(s) involved	Disease
Type I	αl(I) α2(I)	Osteogenesis imperfect Ehlers–Danlos syndrome types I, II, VIIA, VIIB Osteoporosis
Type II	αl(II)	Osteoarthrosis Chondrodysplasias, including Achondrogenesis II Hypochondrogenesis Spondyloepiphyseal dysplasia Spondyloepimetaphyseal dysplasia Kneist syndrome Wagner syndrome Stickler syndrome
Type III	αl(III)	Arterial (familial) aneurysm Ehlers–Danlos syndrome type IV
Type IV	α3(IV)α4(IV)α5(IV) α5(IV)α6(IV)	Alport syndrome Alport syndrome(DOL, GL)
Type V	αl(V)α2(V)	Ehlers–Danlos syndrome types I and II
Type VI	αl(VI)α2(VI)α3(VI)	Bethlem myopathy Ullrich congenital muscular dystrophy
Type VII	αl(VII)	Dystrophic epidermolysis bullosa
Type VIII	α2(VIII)	Corneal endothelial dystrophy
Type IX	αl(IX)α2(IX)α3(IX)	Multiple epiphyseal dysplasia Intervertebral disc disease Osteoarthrosis
Type X	αl(X)	Chondrodysplasia Schmid metaphyseal chondrodysplasia
Type XI	α(XI)α2(Xl)α3(XI)	Nonsyndromic hearing loss Osteoarthrosis Chondrodysplasias, including Stickler syndrome Marshall syndrome Otospondylomegaepiphyseal dysplasia

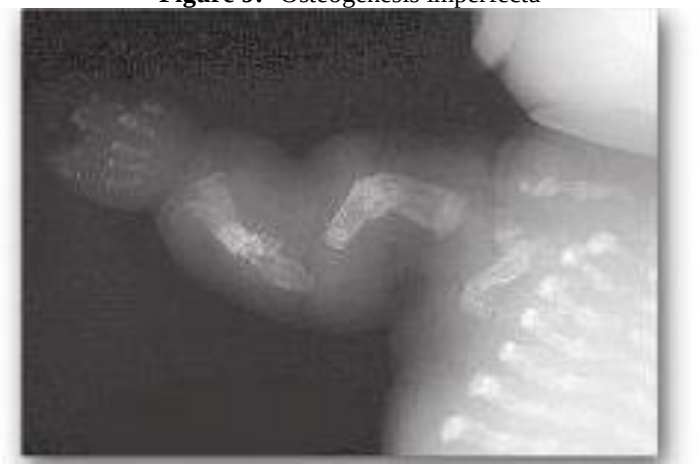
Type XV	αl(XV)	Skeletal myopathy (possible)
Type XVII	αl(XVII)	Generalized atrophic benign epidermolysis bullosa
Type XVIII	αl(XVIII)	Knobloch syndrome

Source: Talwar and Srivastava

Osteogenesis Imperfecta:-

Osteogenesis imperfecta, is also called "brittle bone disease" (Fig. 9). The estimated prevalence is 1/10000 and 1/20000. The characteristics of the disease are enormously fragile bones, reduced bone mass, blue sclera, dentinogenesis imperfecta, hearing loss, and scoliosis. The bone fragility in this disease is connected with the reduced bone mass, degenerated organization of bone tissue as well as with the altered bone geometry in size and shape (Cole 1994: 75).

Figure 9:- Osteogenesis imperfecta



Source: Harvey

The disease is classified according to the defects in the collagen gene. Firstly the disease was divided into four groups. However, the new types of osteogenesis imperfecta were discovered in the recent years, and today the disease has eight groups. Most of the cases are connected with the mutations in two genes encoding the proalpha1 or proalpha2 polypeptide chains of type I collagen. A small part of these diseases origins from a mutation in a cartilage protein or the expression of 3-prolyl-hydroxylase (Burnei G. et al. 2008: 360).

The disease forms may vary from normal to lethal (Gajko-Galicka 1999: 435). If the mutations affect the amount of type I collagen, that usually occurs in case of type I osteogenesis imperfecta, the disease will have mild forms. Mutations in COL1A1 or COL1A2 genes lead to the more severe and lethal forms. The most common forms of this disease are explained by the process when during collagen synthesis the glycine is substituted with a bigger amino acid (Burnei G. et al. 2008: 362). Type VII osteogenesis imperfecta is connected with the mutations in "cartilage-associated protein" gene. The other types of the disease are related with the processes when collagen is not enough of high quality or quantity (Burnei G. et al. 2008: 362).

Osteogenesis imperfecta has different symtoms and can be seen in every age. That is why it is hard to diagnose the disease (Burnei G. et al. 2008: 363). Prenatal diagnosis can be made using clinical, radiographic, biochemical or genetic methods; the rest are diagnosed after birth (Burnei G. et al. 2008: 363).

The treatment of osteogenesis imperfecta is only symptomatic. The nonsurgical treatment includes physical therapy and rehabilitation for strengthening of muscles and improvement of joint mobility. The surgical treatment (insertion of the metal rods) and drugs can be used for increasing of bone strength (Burnei G. et al. 2008: 364). Bisphosphonates are the main medicine that give is substantial improvements for young persons as well as increase patient quality of life (Burnei G. et al. 2008: 365). A potent inhibitor of bone resorption drug and growth hormone become the other option of treatment in recent years (Burnei G. et al. 2008: 365). The studies of somatic gene therapy that could be helpful for the inactivation of the mutations are still in progress.

Ehlers-Danlos Syndrome:-

Ehlers-Danlos syndrome is the disorder of inherited connective tissue that have different forms. The estimated occurrence of Ehlers-Danlos syndrome varies from 1/10000 to 1/25000 (Germain 1995: 190). In the past there were found at least 10 types of the disease. It was classified based upon genetic, biochemical and clinical features. Modern classification is based on the description of the symptoms. The main characteristics of the syndrome are fragile and tender skin, easy bruising, hypermobile joints and atrophic injury (Fig. 10). The disease is caused by the defects in structure, production and interaction of collagen with the other proteins. About 50 % of the cases are connected with the mutations in the COL5A1 and COL5A2 genes encoding the α1 and α2 chains of type V collagen (Myllyharju and Kivirikko 2001: 14).

Figure 10:- Ehlers-Danlos syndrome

Source: Harvey

Types I and II are classical forms of Ehlers-Danlos syndrome. These types are caused be the mutations connected with the collagen V synthesis. Type I has more severe forms of skin involvement comparing type II. The hypermobility can be present for these types (Myllyharju and Kivirikko 2001: 14).

The hypermobility type got its name by the main symptom that occurs in this case. The patient also experiences dislocations and subluxations with or without trauma that causes very painful sensation. The additional problem is early osteoarthritis. Skin involvement does not have severe forms (Myllyharju and Kivirikko 2001: 14).

Vascular type of Ehlers-Danlos syndrome is one of the most serious forms. In this case, blood vessels and organs are very fragile that may lead to its easy rupture. The bruises without trauma and easy bruising also arises during this form of disease. This form lead to the severe complications for the most of patients by the age of 40 (Germain 1995: 192).

Kyphoscoliosis form is caused by the deficiency of lysyl hydroxylase. The typical symptoms are scoliosis, muscle weakness and fragile eyes. It is very rare form. Dermatosparaxis is another rare form, which is characterized by fragile and sagging skin. Arthrochalasia is also very rare. Its main characteristic is serious hypermobility (two times more serious comparing hypermobility type) (Germain 1995: 192).

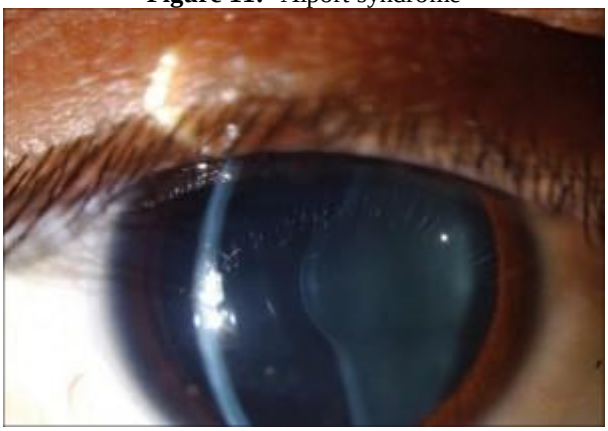
The diagnosis foresees the study of medical history, clinical observations, performing of diagnostic tests, DNA and biochemical studies. The treatment is mostly symptomatic. Usually, it includes monitoring of the cardiovascular system, physiotherapy, occupational therapy, and utilization of orthopaedic instruments. Constant observation is a very important part of the treatment. Surgical procedures, like joint debridement, tendon replacements, capsulorraphy and arthroplasty may be used in case of serious dislocations (Germain 1995: 193).

Alport Syndrome:-

Alport syndrome is characterized by glomerulonephritis accompanied with the hearing loss and eye problems (Fig. 11). It is caused by deletion mutations in COL4A5 and COL4A6 genes or COL4A3 and COL4A4 genes that encode the α3(IV) and α4(IV)-chains. Alport syndrome occurs in 1 case for the 5000 persons (Kashtan 1999: 338). The type

IV collagen network formed by α3, α4 and α5(IV)-chains is lost during the disease (Kashtan 1999: 340). The damage of collagen IV due leads to the dysfunction of bound epithelium and to organ destruction (Kashtan 1999: 341).

Figure 11:- Alport syndrome



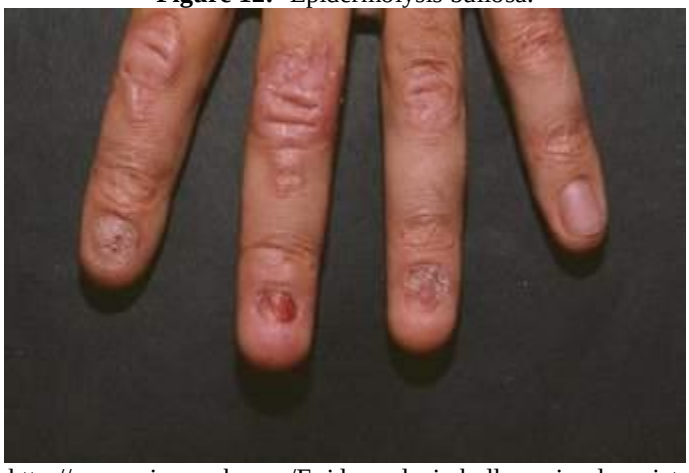
Source: http://www.hxbenefit.com/alport-syndrome.html

The treatment of the Alport syndrome is symptomatic. The symptoms may be treated by ACE inhibitors. The dialysis or kidney transplantation are used when the kidney disease is developed. However, transplantation is not always successful because normal collagen of the transplant cannot be recognized (Kashtan 1999: 345).

Epidermolysis Bullosa:-

Epidermolysis bullosa is a connective tissue disease that causes blisters on the skin (Fig. 12). It occurs 1 case per 50000 persons. The anchoring between dermis and epidermis are disrupted that leads to skin fragility. The defects of 10 genes (or about 300 mutations) are responsible for the different types of this disease (Eady 2001: 638).

Figure 12:- Epidermolysis bullosa.



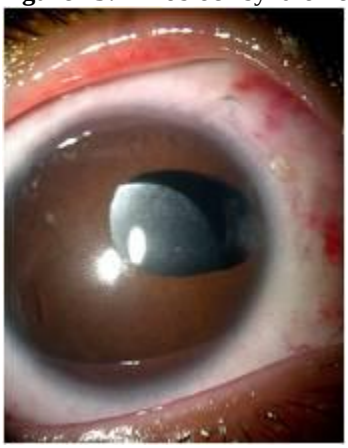
Source:- http://www.picsearch.com/Epidermolysis-bullosa-simplex-pictures.html

There are three main types of epidermolysis bullosa: epidermolysis bullosa simplex, junctional epidermolysis bullosa, and dystrophic epidermolysis bullosa. Epidermolysis bullosa simplex causes blisters on the hands and feet. In this case, keratin genes KRT5 and KRT4 are affected. Junctional epidermolysis bullosa is characterized by blister formation within the basement membrane zone. Dystrophic epidermolysis bullosa affect both organs and skin (Eady 2001: 638).

Current treatment of the disease includes nurturing of the skin and other organs, infection cure for chronic wounds, nutritional support. In some cases, the surgical treatment that foresees tissue transplantation is used (Eady 2001: 640).

Knobloch Syndrome:-
Knobloch syndrome is caused by the mutation of collagen XVIII gene. These mutations lead to the loss of one or all collagen COL18A1 isoforms or endostatin (O'Connell, Toner and Murphy 2009: 213). The main characteristics of the disease are high myopia, vitreoretinal degeneration, occipital bone damage, and congenital encephalocele. The risk to get the disease increases if the family member suffered from the syndrome (O'Connell, Toner and Murphy 2009: 214).

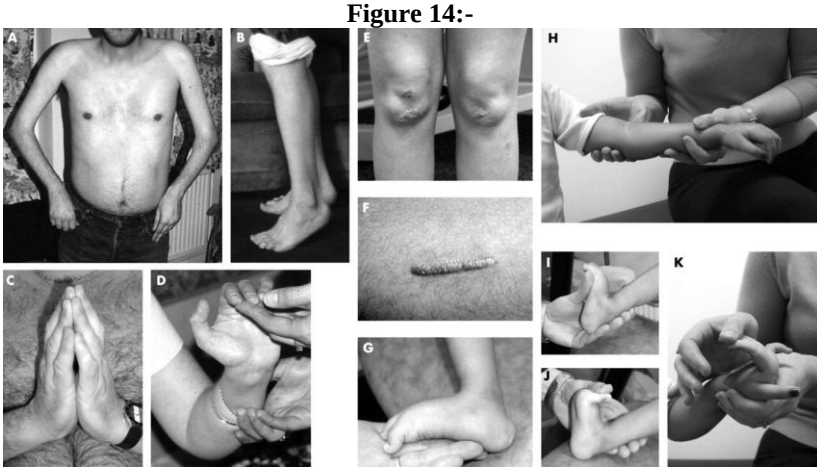
Figure 13:- Knobloch syndrome



Source: https://www.google.com.ua/search?q=knobloch+syndrome+pictures

Bethlem Myopathy:-
Bethlem myopathy is a form of muscular dystrophy (Fig. 14). It is comparatively mild disease. Bethlem myopathy is caused by the mutation of the type VI collagen genes. This collagen is the component of the connecting cells and extracellular matrix. The disease develops very slowly, and the most of patients feels first symptoms at the age of 50 years (Lampe and Bushby 2005: 680).

Figure 14:-



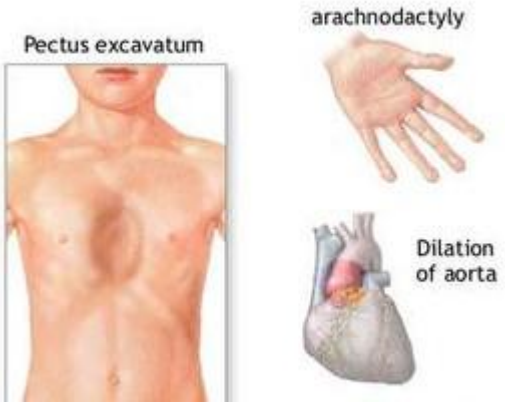
Source: https://www.google.com.ua/search?q=Bethlem+Myopathy+pictures

Marfan's syndrome:-
Marfan's syndrome is the disease of the connective tissue caused by the misfolding of fibrillin-1. This protein is coded by the FBN1 gene. The syndrome occurs approximately 1 in 5000 cases. There are more than 500 FBN1 mutations for the syndrome (Nollen and Mulder 2004: 103). The diagnosis includes study of the family history and the using of Ghent nosology. However, to get the definite diagnosis, genetic test should be executed (Nollen and Mulder 2004: 105).

Its main characteristics of the disease are aortic dilatation that leads to the aortic valve failure, prolapsus and failure of mitral valve, lens dislocation and myopia. The patients with the Marfan's syndrome have long and thin body, long

limbs due to excessive bone growth, as well as arachnodactyly, chest deformations, defects of the skeletal system, skin, nervous system and lungs, and sometimes scoliosis (Fig.15) (Nollen and Mulder 2004: 106).

Figure 15:- Marfan's syndrome



Source: http://www.picsearch.com/Marfan-syndrome-pictures.html

Typically, persons with the Marfan's syndrome dies of the rupture of the aortic root. Furthermore, this syndrome can lead to various surgical pathologies such as hernia, ileus and abdominal vein aneurysms. All the pathologies can be life-threatening (Nollen and Mulder 2004: 107).

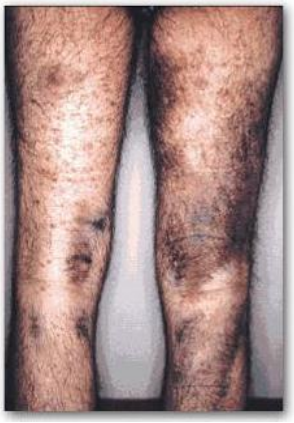
As for the rest of genetic diseases, Marfan's syndrome has no cure. However, proper treatment can increase the life span of persons with this disorder. Primarily, aortic dilation and damage to heart valves should be controlled. Drugs for the elimination of the arrhythmia and minimizing blood pressure are used for this purpose. Vascular surgery may be also helpful. Pain medicines and muscle relaxants as well as physiotherapy are used for the treatment of skeletal symptoms of the disease (Nollen and Mulder 2004: 107).

Disorders without genetic heritage:-

Some diseases has no genetic heritage. Scurvy and osteoporosis are the most common. Furthermore, some types of viruses may affect the collagen structure attaching the fibres (Talwar and Srivastava 2006: 101).

Scurvy is caused by the deficiency of vitamin C. It is an important component for the stage of proline and lysine hydroxylation. If this stage is not performed properly the collagen will have hydrogen bonds. The stricture of fibrils become weak (Myllyharju and Kivirikko 2001: 19). Capillaries made of such collagen become fragile that leads to bleeding. Easy bruising, poor wound healing and bone pain are additional symptoms (Fig. 16). As the human body does not synthesize vitamin C, its deficiency should be supplemented by the proper dietary. In this case, the disease can be completely cured (Talwar and Srivastava 2006: 101).

Figure 16:- Scurvy



Source: Harvey

Osteoporosis is the disease connected with the loosing of bone mass and density (Fig. 17). It may arise due to aging or use of medicines like glucocorticoids. Hormonal factor can also play an important role. During the osteoporosis the balance between bone resorption and bone formation is disrupted. The proper nutrition, healthy lifestyle (especially cessation of smoking and alcohol consumption), bisphosphonates and hormonal therapy may prevent the disease or manage it (Myllyharju and Kivirikko 2001: 19).

Figure 17:- Osteoporosis

Source: http://www.medicinenet.com/image-ollection/osteoporosis_progression_picture/picture.htm

Conclusion:-

Collagen is one of the most important proteins in the body. It is the main component of the extracellular matrix. Its structure differs from the other proteins. The main feature of collagen is the ability to create fibrillar structure. The presence of hydrolysed peptide residues of proline and lysine as well as sequence of where each third amino acid is glycine permits to create the structure of the triple helix. Hydrolyzation and glycosylation assist the creation of the large fibres. Collagen synthesis is coded be the certain genes and includes intracellular and extracellular stages. During intracellular stage peptide chains are formed, and pro-collagen is synthesised. The fibrillar structures are forming during the extracellular stage. Apart from the fibrillar structure, there are also sheet, FACIT, sponge structures of collagen, as well as structures with anchoring fibrils. The structure of collagen depends on the presence of non-collagen domains and its sequence.

Collagen synthesis can be disrupted mostly due to the various gene mutation. Each mutation effects on the synthesis of the certain collagen type leading to the serious diseases of connective tissue and bones. Osteogenesis imperfecta, Ehlers-Danlos syndrome, Alport syndrome, Bethlem myopathy, epidermolysis bullosa, Knobloch syndrome and Marfan's syndrome are the most known. Marfan's syndrome is the most common syndromes (1 case for every 5000 persons). The treatment of diseases caused by gene mutation can be only symptomatic. The diseases like osteoporosis and scurvy are not connected with the genetic heritage. Proper therapy and nutrition as well as healthy lifestyle give possibility to cure these disorders.

Scientists discovered 28 collagen types. Enough information about synthesis of collagen and its structure is obtained. However, there still a lot of issues that should be studied. Further researches will permit to understand the details of collagen formation. It will give the possibility create new materials with collagen structure for medical and industrial applications, as well as to improve the treatment of disorders connected with the collagen synthesis.

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